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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,180	OHKAWA ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,25-28,33 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-16 and 18* is/are allowed.

6)☒ Claim(s) *17,19,25-28,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to amendments filed on 11/6/03. Applicant has amended claims 2, 3, 9-16, 25, and 26. Claims 33 and 34 are new. There are twenty-five claims pending and twenty-five under consideration. Claims 1-17 are compound claims. Claim 19 is a composition claim. Claims 25-28, 33, and 34 are use claims. Claim 19 is a method of synthesis claim. This is the first action on the merits. The application concerns some furo[2,3-f]indole compounds, compositions, and uses thereof.

Information Disclosure Statement

2. Applicants' comments concerning the IDS of 3/11/03 are noted. The present application has converted to a scanned form. The cover letter dated 3/14/03 concerning the IDS is present in the file but there is no PTO-1449 form. Two scanned articles are present in the file, one from "Free Radical Biology" and the other from "J. Med. Chem." are present in the file but are not referenced on any present IDS form. The USPTO scanning team has been notified of the problem.

Response to Amendment

3. Applicants' amendments concerning substituted overcome the indefiniteness rejection made in point #2 of the previous office action. Applicants point to the passage spanning page 32, lines 22 to page 33, line 24 defining "acyl". This is persuasive and the indefiniteness rejection made in point #3 is withdrawn. Applicants point to page 31, line 18 to page 32, line 4 as defining "cyclic amino

group". This is persuasive and the indefiniteness rejection made in point #4 is withdrawn.

4. The declaration under 37 CFR 1.132 filed 11/6/03 by Dr. Hashimoto is insufficient to overcome the rejection of claims 25-28 based upon lack of enablement as set forth in the last Office action. The issue is not the ability of Applicants compounds to inhibit lipid peroxidation *in vitro* but rather the ability of Applicants compounds to treat and prevent human disease in the clinic. See *Ex parte Jovanovics,* 211 USPQ 907, *In re Langer,* 183 USPQ 288, *Hoffman v. Klaus,* 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

Where is the evidence that this single *in vitro* assay possesses the required correlation to clinical efficacy against any specific disease. Case law is clear on this point. In an unpredictable art, such as cardiovascular, neurodegenerative, urinary, or restenosis disease therapy, *in vitro* assays may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy.

The issue in *Ex parte Balzarini* 21 USPQ2d 1892 concerned HIV treatment and the Board of Patent Appeals and Interferences wrote "While the in *vitro* testing performed on these anti-viral compounds appears to be useful as a screening tool in order to determine which of these anti-viral compounds are candidates for further testing to determine if they possess in *vivo* utility, the in *vitro* tests were not predictive of in *vivo* efficacy."

The issue in *Fujikawa v. Wattanasin* 39 USPQ2d 1895 was adequacy of *in vitro* testing of inhibitors of cholesterol biosynthesis and U.S. Court of Appeals Federal Circuit wrote "*in vitro* results, in combination with a known correlation between such in *vitro* results and in *vivo* activity, may be sufficient to establish practical utility". Such a correlation does not exist in the art of lipid peroxidation inhibition pharmacology.

In a peripheral issue involving assaying insulin-like growth factor-I ("IGF-I") in *Genentech Inc. v. Chiron Corp.* 55 USPQ2d 1636, U.S. Court of Appeals Federal Circuit wrote "by the critical date, ... [s]pecific binding in an RRA was known by those skilled in the art to be reasonably correlated with the *in vivo* biological activity of IGF-I."

In *Ex parte Bhide* 42 USPQ2d 1441, the Board of Patent Appeals and Interferences wrote "While in *vitro* or in *vivo* tests would not be the only possible

way to overcome our basis for questioning applicants' utility, in *vitro* or in *vivo* tests certainly would provide relevant evidence". The issue in the present case is not the utility of applicants' compounds, which was at issue in *Ex parte Bhide* 42 USPQ2d 1441, but rather the narrower issue of enablement for claims drawn to the treatment of all cardiovascular, neurodegenerative, urinary, or restenosis disease. Since such a claim is inherently not credible, the standard of proof required for such an assertion must be high.

In a case concerning a DNA sequence encoding a mature human IL-3 protein, *Ex parte Anderson* 30 USPQ2d 1866, the Board of Patent Appeals and Interferences wrote in passing "We question whether one skilled in the art would accept appellants' *in vitro* test as predictive of *in vivo* results and whether one skilled in the art would know how to use the Pro (8) protein made. ... Should the claims of this application be prosecuted further in a continuing application we urge the examiner to consider the enablement and utility aspects of patentability."

In an anti-tumor application, *Ex parte Aggarwal* 23 USPQ2d 1334, the Board of Patent Appeals and Interferences wrote "there is considerable doubt that those skilled in the art would be willing to accept appellants' in *vitro* tests and in *vivo* tests as established models predictive of utility against tumors in humans. See *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 The examiner had more than adequate

reason to doubt the objective truth of the broad statement of utility set forth in appellants' specification."

In the most definitive finding on this issue of the adequacy of *in vitro* assays for clinical claims, *Ex parte Stevens* 16 USPQ2d 1379 the Board of Patent Appeals and Interferences wrote "The examiner's position is based on the supposition that the facts described above evidence a prima facie case of nonenablement with regard to the disclosed utility in light of all the applicable legal precedents. Where as here, the disclosed utility is the treatment of cancer, we agree with this supposition. The examiner has cited Ex *parte Busse*, 1 USPQ2d 1908. In that case, the Board of Patent Appeals and Interferences reviewed the relevant prior decisions of its reviewing court. We shall not repeat those citations here. Suffice it to say that in every cited case the narrow issue involved was whether or not the evidence of record was based on *in vivo* or *in vitro* studies which were generally recognized by those of ordinary skill in the art as being reasonably predictive of success in the practical utility under consideration, i.e., human or, at least, mammalian therapy."

In a vaccine case, *Ex parte Maas* 14 USPQ2d 1762, the Board of Patent Appeals and Interferences wrote "First, although appellants' specification describes certain in *vitro* experiments, there is no correlation on this record between in *vitro*

experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in *vitro* studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals. The burden is on appellants to establish the significance of the in *vitro* experiments set forth in their specification."

Claim Rejections - 35 USC § 112

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 17, 19, and 25-28 remain rejected and claims 33 and 34 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "prodrug" in each of these claims is indefinite. What are the structures of these prodrugs? The issue on second paragraph is whether the structures of the claimed compounds are clearly defined. Applicants' "prodrugs" are molecules whose structure lie outside the subject matter of the formula of claim 1, but upon metabolism in the body are converted to active compounds falling within the structural scope of formula 1. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug".

Applicants point to pages 119 and 120 as the specification as providing the structural definition of the term. This is not persuasive for four reasons. Firstly, the passage cited uses open language, "maybe for example". Are the alanylated compounds the claimed prodrugs or not? Is the palmitoyl ester of a claimed alcohol such a claimed prodrug or not? We know what the concept of prodrug entails. What we do not know is what specific compounds Applicants claim. Secondly, passage cited a foreign language reference pages 163 to 198 in Molecular Designing in Vol. 7 of 'Pharmaceutical Development (IMAKUHIN-SO-KAIHATSU) that is not available to the Examiner. Thirdly, none of the references teaches how to make prodrugs of Applicants compounds or even of compounds closely related by structure to Applicants'. Fourthly, finding a prodrug is a largely empirical exercise. Predicting if a certain palmitoyl ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Do all the derivates cited in the passage meet the limitations of prodrug or not?

6. Claims 17, 19, and 25-28 remain rejected and claims 33 and 34 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of claimed compounds, does not reasonably

provide enablement for making prodrugs generally. The specification does not enable any person skilled in the arts of synthetic pharmaceutical chemists and metabolism, to use the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical

trial setting passes the threshold of undue experimentation. A large degree of experimentation is necessary. b) There is no direction in the specification to the determination of whether a compound is a prodrug nor is there any direction as to possible structures of such compounds. c) There is no working example of a prodrug of a compound formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetics of substances in the human body. e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. g) The lack of predictability in finding prodrugs was discussed above. h) The breadth of the claims includes all of the hundreds of

thousands of compounds of the formula given in claim 1 as well as the presently unknown list potential prodrug derivatives embraced by claim 17.

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

Applicants made no analysis of the *Ex parte Formal* enablement factors cited by the Examiner. Applicants stated only "Applicants hereby incorporate their arguments found in Sec. VII. above in response to this rejection."

7. Claims 17, 19, and 25-28 remain rejected and claims 33 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for synthesizing salts of claimed compounds, does not reasonably provide enablement for synthesizing prodrugs generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The specification in lines 9-10, page 120 gives directions for preparing the "prodrugs" of the claimed compounds. This passage states that "a per se known method" is to be used. What is a *per se* known method? Since the structures of these "prodrugs" are uncertain, direction for their preparation must also be unclear.

Applicants made no remarks concerning how to synthesize their prodrugs.

8. Claims 25-28 remain rejected and claim 34 is newly under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cranial trauma, does not reasonably provide enablement for treating cerebrovascular impairment, dysuria, urinary incontentance, restenosis, of neurodegenerative diseases. The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above. a) Determining if any particular claimed compound would treat any particular cardiovascular, neurodegenerative, urinary, or restenosis disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases described below, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large degree of experimentation. b) There is a *single in vitro* assay described in the passage spanning line 22, page 188 to line 5, page 190 with data for two species but it is unclear if this assay is correlated to the claimed diseases. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in lipoperoxidase inhibitors is discussed by Delanty (Arch. Neurol). The treatment of

traumatic CNS injury with an inhibitor of lipoperoxide production is found in the third complete paragraph, second column page 1268. The lack of clinical efficacy for stroke, neurodegenerative diseases, AIDS, and epilepsy with such inhibitors is found in the passage spanning pages 1267 to 1269. With reference to claim 26, Applicants should note the first sentence of the abstract of Solin (Kidney Int.), "little is known of their significance and respective scavenger systems in human glomerular diseases". Both dysuria and urinary incontinence are glomerular diseases.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the thousands of compounds of claim 1. In addition the term "neurodegenerative disease" covers a broad array of different disorders that have different modes of action and different origins. The term covers such diverse disorders as Alzheimer's Disease; Parkinson's Disease; ALS and variants such as forms of ALS-PDC; Gerstmann-Straussler-Scheinker Disease (GSS); Pick's Disease; Diffuse Lewy Body Disease; Hallervordon-Spatz disease;

progressive familiar myoclonic epilepsy; Corticodentatonigral degeneration; progressive supranuclear palsy (Steele-Richardson-Olszewski); Huntington's disease; more than a dozen dementias collectively called "frontotemporal dementia and Parkinsonism linked to chromosome 17" (FTDP-17); Tourette's syndrome; Shy-Drager syndrome; Friedrich's ataxia and other spinocerebellar degenerations; Olivopontocerebellar atrophy (OPCA); spasmotic torticollis; Striatonigral degeneration; various types of torsion dystonia; certain spinal muscular atrophies, such as Werdnig-Hoffmann and Wohlfart-Kugelberg-Welander; Hereditary spastic paraplegia, Primary lateral sclerosis; peroneal muscular atrophy (Charcot-Marie-Tooth); Creutzfeldt-Jakob Disease (CJD); Hypertrophic interstitial polyneuropathy (Dejerine-Sottas); retinitis pigmentosa; Leber's Disease; and Hypertrophic interstitial polyneuropathy. These exhibit a very broad range of effects and origins. For example, some give progressive dementia without other prominent neurological signs, such as Alzheimer's disease, whereas other dementias have such signs, such as Diffuse Lewy Body Disease. Some give muscular wasting without sensory changes, e.g. ALS, and some do have the sensory changes such as Werdnig-Hoffmann. Some are abnormalities of posture, movement, or speech, such as Striatonigral degeneration, and other are progressive ataxias, such as OPCA. Some are linked to tau mutations, such as Alzheimer's disease and FTDP-

17, and other such as Parkinson's clearly do not. Some affect only vision such as retinitis pigmentosa. Even within those that fall into the same category of effects, there are often striking differences. For example, Alzheimer's disease and Pick's disease both give progressive dementia without other prominent neurological signs. However, the characteristic Alzheimer's neurofibrillary tangles are not seen in Pick's Disease, which has straight fibrils, as opposed to the paired helical filaments of Alzheimer's disease. Pick's Disease gives lobal atrophy, not seen in Alzheimer's disease. There are differences in origins, even with what little is known. Thus, among progressive dementias, CJD is definitely caused by an infectious agent; so far as can be determined, this is not so for Huntington's disease. Even among the hereditary disorders, the origins are different. Thus, FTDP-17 comes from chromosome 17, Huntington's disease from 4, and the neurodegenerative disorder that people with Down's syndrome develop later in life is presumably connected in some way to 21.

The great majority of these have no treatment at all, and of those that do, none or virtually none have been treated with such inhibitors as are disclosed here. The great diversity of diseases falling within the "neurodegenerative disease" category means that it is contrary to medical understanding that any agent (let alone a genus of trillions of compounds) could be generally effective against such

diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Further, what little success there has been does not point in this direction. Thus, what very few treatments that the massive research effort on Alzheimer's disease has produced are means of providing acetylcholinesterase inhibition, unrelated to the mechanism of action in this case. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

9. Claims 25-28 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cranial trauma, does not reasonably provide enablement for preventing any diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only

established prophylactics are vaccines not the furo[2,3-f]indole compounds such as present here. In addition, it is presumed that "prevention" of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

The Examiner suggests deletion of the word "preventing".

Applicants relied upon the declaration of Dr. Hashimoto to support their claims for enablement. That declaration was discussed above.

Allowable Subject Matter

10. Claims 1-16 and 18 allowed.

Conclusion

11. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. After February 9, 2004, the Examiner may be reached at (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any

inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK